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10/634,145	08/04/2003	Chew Kiat Heng	NAA 0018 PA/41049.20	5097

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EXAMINER	
WHALEY, PABLO S	
ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/634,145	HENG ET AL.	
	Examiner	Art Unit	
	PABLO WHALEY	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 17-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims Under Examination

Claims 1-15 and 17-30 are pending.

Claim 16 is cancelled.

Withdrawn Rejections

The rejection of claims 1-15 and 17-30 under 35 U.S.C. 101 for non-statutory subject matter is withdrawn in view of applicant's amendments to claims 1, 21, and 28, filed 03/13/2008, which now is directed to presenting data to a user.

The rejection of claims 1, 2, 3, 9, 19, 20, 21, 23, and 28-30 under 35 U.S.C. 103(a) as being made obvious by Dodds et al. (US 6,287,254; Issued: Sept. 11, 2001), in view of Luciano et al. (US 6, 063,028; Issued May 16, 2000), is withdrawn in view of applicant's amendments to claims 1, 21, and 28, and arguments, filed 03/13/2008, that combination of cited references does not teach optimizing the parameters of a risk prediction model wherein each deviate is weighted in said sum by a weight associated with, and indicating a statistical significance of, that set for which said deviate has been calculated, and wherein the weights used to weight said deviates are determined with a constraint that said weights associated with sets of said data having like genetic data are the same.

The rejection of claims 1-13, 15, 17-26, 28, 29, and 30 under 35 U.S.C. 103(a) as being made obvious by Dodds et al. (US 6,287,254; Issued: Sept. 11, 2001), in view of Tibshirani (Statistics In Medicine, 1997, Vol. 16, p.385-395) and Nelson et al. (J Clin Epidemiol, 1998, Vol. 51, No. 3, pp. 199–209), is withdrawn

in view of applicant's amendments to claims 1, 21, and 28, and arguments, filed 03/13/2008, that combination of cited references does not teach optimizing the parameters of a risk prediction model wherein each deviate is weighted in said sum by a weight associated with, and indicating a statistical significance of, that set for which said deviate has been calculated, and wherein the weights used to weight said deviates are determined with a constraint that said weights associated with sets of said data having like genetic data are the same.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11, 18-23, 28, 29, and 30 are rejected under 35 U.S.C. 103(a) as being made obvious by Tibshirani (Statistics In Medicine, 1997, Vol. 16, p.385-395), in view of Nguyen et al. (Bioinformatics, 2002, Vol. 18, No. 12, p.1625-1632), in view of Mariani et al. (Breast Cancer Research and Treatment, 1997, Vol. 44, p. 167–178), and in view of Walters (What is a Cox Model, Copyright 2001, Vol. 1, No. 10, p.1-8)

Applicants' amendment filed 03/13/2008 amended claims 1, 21, and 28, which now recite steps for (i) collecting non-genetic, genetic, and disease status data; (ii) storing a candidate statistical model for calculating disease risk as a function of non-genetic data; and (iii) optimizing model parameters by fitting, wherein fitting comprises calculating a sum of weighted deviates, wherein each deviate is weighted in said sum by a weight associated with, and indicating a statistical significance of, that set for which said deviate has been calculated, and wherein the weights used to weight said deviates are determined with a constraint that said weights associated with sets of said data having like genetic data are the same.

Tibshirani teaches a computer-implemented method for determining variables for a Cox proportional-hazard model [Abstract]. In particular, Tibshirani teaches collecting a plurality of data sets associated with cancer comprising Karnofsky scores, age, sex, state of disease, cell type, treatment, etc. [p.387-389], which shows 'indicators of disease status', and 'non-genetic' data. Tibshirani teaches a general Cox statistical model for calculating risk [Section 1, Equations 1 and 2] using non-genetic data [p.387, Example 3], wherein the program is stored on a computer [p.386, Section 2]. Tibshirani teaches optimizing model parameters by calculating deviations in data sets using seventeen variables and using full, stepwise, and Lasso models (i.e. which incorporates minimized weighted values as described in Section 2) for data simulations [p.390, Table I, p.391, Section 5.2, and Fig. 2]. Tibshirani teaches optimization of model parameters via an argmin function (i.e. target function) [p.386, ¶ 1]. Tibshirani teaches grouping of data indicative of a plurality of factors, wherein groups include values of 0 and 1,

determining scores for each variable [Table I], and discarding missing values of data [p.389, ¶ 1]. Tibshirani teaches the comparison of models after simulation to select and output an optimum model with optimum parameters, wherein one model uses a different number of parameters [Table I], and shows selecting the appropriate number of coefficients [Table 1,and p.391, Section 5.1].

Tibshirani does not teach collecting genetic data, as in claims 1, 21, and 28.

Tibshirani does not specifically teach indicating a statistical significance associated with calculated weighted deviates, as in claims 1, 21, and 28.

Tibshirani does not specifically teach calculating weights determined with a constraint that weights associated with sets of data having like genetic data are the same, as in claims 1, 2, 3, 19, 20, 21, and 28-30. However, this limitation would have been obvious to one of ordinary skill in the art, since Tibshirani shows that weights associated with like data sets have the same values [p.387, lines 12-17].

Walters teaches a review of predictive regression models. In particular, Walters teaches the Cox regression model for describing a relationship between a plurality of different types of data, equations for calculating the predicted risk (i.e. weighted deviates) based upon a sum of weights [p.4, Col. 1 and Table 2], and determining the statistical significance of each of the variables [p. 4, Col. 2, last ¶], as in claims 1, 21, and 28.

Nguyen teaches a method for predicting cancer survival using hazard regression models applied to microarray data (i.e. genetic data) [Abstract, p.1626, Methods], and teaches the optimization of model parameters by fitting data [p.1626, Col. 2, ¶3, p.1630, Col. 1, ¶2, ¶3, and Fig. 1], as in claims 1, 21, and 28. Nguyen suggests this method enables scientists to improve the prediction of cancer survival probabilities using high-dimension data [p.1630, Discussion].

Mariani teaches the analysis of non-genetic data using Cox hazard models and neural network models [Abstract and p.175-176, Appendix], and suggests that risk factors comprise a genetic component [p.173, Col. 1, ¶3] Mariani also teaches hazard equations for describing coefficients as a linear

combination of weights [Col. 175, Col. 2 and p.176, Col. 1] and optimization of weights based on differences between observed and predicted values [p.176, Col. 1, ¶1]. In Mariani, suggests a need for flexible models that allow for the integration of different types of predictive factors, especially in the case of low predictiveness [p.175, Col.1].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the statistical model to analyze non-genetic data taught by Tibshirani in combination with genetic data of Nguyen, since Nguyen shows that Cox regression analysis is widely used in biological and medical research [p.1630, Col. 2, Discussion] and since Mariani suggests that risk factors comprise a genetic component [p.173, Col. 1, ¶3]. One of ordinary skill in the art would have been motivated to analyze non-genetic data in combination genetic data in order to develop flexible models that allow for the integration of different types of predictive factors, especially in the case of low predictiveness, as suggested by Mariani [p.175, Col. 1].

Claims 1-15 and 17- 30 are rejected under 35 U.S.C. 103(a) as being made obvious by Tibshirani (Statistics In Medicine, 1997, Vol. 16, p.385-395), in view of Nguyen et al. (Bioinformatics, 2002, Vol. 18, No. 12, p.1625-1632), in view of Mariani et al. (Breast Cancer Research and Treatment, 1997, Vol. 44, p. 167–178), and in view of Walters (What is a Cox Model, Copyright 2001, Vol. 1, No. 10, p.1-8), as applied to claims 1-11, 18-23, 28, 29, and 30 above, and further in view of Lazzeroni et al. (Proceedings of the Survey Research Methods, 1990, p. 260-265).

Tibshirani, Nguyen, Mariani, and Walters make obvious a computer-implemented for predicting disease risk using genetic and non-genetic data, as set forth above.

Tibshirani, Nguyen, Mariani, and Walters do not specifically teach imputing missing data, as in claim 12, or calculating adjustment factors, as in claims 13, 14, and 27.

Lazzeroni teaches methods for determining the robustness of models using imputation techniques. In particular, Lazzeroni teach imputing missing data based on regression models [Sections 1 and 2], as in claim 12. In addition, Lazzeroni teaches weights that are weighted by adjustment factors that have been calculated in order to correct for possible bias in the population data [p.261, Col. 2, ¶3, and p. 262, Col. 1, ¶1], as in claims 13, 14, and 27. Lazzeroni does not teach the particular equation for calculating adjustment factors based on a ratio between population members, as in claims 14 and 27. However, this limitation would have been obvious to one of ordinary skill in the art since Lazzeroni teaches adjustment factors based on a difference between population members.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention practice the method made obvious by Tibshirani, Nguyen, and Mariani in combination with the analysis methods for imputing missing data and calculating adjustment factors, as taught by Lazzeroni, since Lazzeroni teaches methods for assessing the robustness of linear regression models that use population data [Section 1]. One of ordinary skill in the art would have been motivated to combine the teachings of Lazzeroni in order to improve model accuracy by accounting for model misspecification and possible bias in the predictive data, as suggested by Lazzeroni [p.262, Col. 1, ¶1].

Claims 1-11, 18-26, and 28-30 are rejected under 35 U.S.C. 103(a) as being made obvious by Tibshirani (Statistics In Medicine, 1997, Vol. 16, p.385-395), in view of Nguyen et al. (Bioinformatics, 2002, Vol. 18, No. 12, p.1625-1632), in view of Mariani et al. (Breast Cancer Research and Treatment, 1997, Vol. 44, p. 167–178), and in view of Walters (What is a Cox Model, Copyright 2001, Vol. 1, No. 10, p.1-8), as applied to claims 1-11, 18-23, and 28-30 above, and further in view of Nelson et al. (Journal of Clinical Epidemiology, 1998, Vol. 51, No. 3, pp. 199–209).

Tibshirani, Nguyen, Mariani, and Walters make obvious a computer-implemented for predicting disease risk using genetic and non-genetic data, as set forth above.

Tibshirani, Nguyen, Mariani, and Walters do not specifically teach recursively dividing data, as in claims 24-26.

Nelson teaches a method of partitioning data to determine disease subgroups [Abstract and Fig. 1]. In particular, Nelson teaches the recursive partitioning of data, wherein subjects are assigned to subsets according to a set of predictor variables [Abstract and Fig. 1], and splitting criteria (i.e. Gini indexing) for identifying variables that minimize variance between case (i.e. disease) and control groups (i.e. reference) [p.207 and 208, Appendix A, and Fig. 1], as in claims 24-26. Nelson suggests their method may uncover interactions between predictive variables that may be overlooked in traditional case-control studies [Abstract].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention practice the method made obvious by Tibshirani, Nguyen, and Mariani using recursive partitioning as taught by Nelson et al., since Nelson suggests that recursive partitioning is commonly used for disease prediction [p.201, Col. 1, ¶ 1] and since all teach methods of regression analysis [p.204, Col. 1, ¶ 2]. One of ordinary skill in the art would have been motivated to further analyze the risk variables using the method of Nelson in order to improve model accuracy by accounting for overlooked interactions between predictive variables, as suggested by Nelson [Abstract and p.208, Col. 1, ¶2].

Response to Arguments

Applicants' arguments, filed 03/13/2008, with respect to the rejections of claims 1, 2, 3, 9, 19, 20, 21, 23, and 28-30 under 35 U.S.C. 103(a) and claims 1-13, 15, 17-26, 28, 29, and 30 under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejections have been withdrawn.

However, upon further consideration, a new ground(s) of rejection is made in view of applicant's amendments to claims 1, 21, and 28, directed to optimizing the parameters of a risk prediction model wherein each deviate is weighted in said sum by a weight associated with, and indicating a statistical significance of, that set for which said deviate has been calculated, and wherein the weights used to weight said deviates are determined with a constraint that said weights associated with sets of said data having like genetic data are the same.

Applicants' arguments, filed 03/13/2008, that Tibshirani does not teach any adjustment factor or weight for individual data sets as in claims 14 or 27 have been considered but are moot in view of the new ground of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Pablo S. Whaley/

Patent Examiner

Art Unit 1631

/John S. Brusca/

Primary Examiner, Art Unit 1631